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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,876	06/08/2006	Roy Larsen	50147/010001	9168

21559 7590 09/27/2011

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
09/27/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/552,876	LARSEN ET AL.	
	Examiner	Art Unit	
	MELISSA PERREIRA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *14-17* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *14-17* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 14-17 are pending in the application.

Response to Arguments

2. Applicant's arguments filed 8/2/11 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacques et al. (*J. Alloys Compds.* **1994**, *213/214*, 286-289; abstract) in view of Deal et al. (*J. Med. Chem.* **1999**, *42*, 2988-2992) and Larsen et al. (US 2001/0008625A1) and in further view of Ma et al. (US 2003/0086868A1) as stated in the office action mailed 2/2/11.

5. Applicant asserts that no specific isotope of Thorium is mentioned in the abstract of Jacques et al. Applicants submit that the disclosure does not provide a clear and unambiguous disclosure of which isotope was used. In the absence of this teaching, it appears likely that the most abundant thorium isotope, Thorium-232, would have been used. Thorium- 232 has a half-life of 14 billion years and, given the long half-life, radioactive decay of thorium is not a factor in the complexes of Jacques. Accordingly,

Applicants submit that the abstract of Jacques provides no information on the abilities of the DOTA and HEHA macrocycles to effectively encapsulate Thorium-227 and its decay product Radium-223.

6. The reference of Jacques et al. was not explicitly used to teach of thorium-227 but was specifically used to teach that polyaza polycarboxylic macrocycles, DOTA and HEHA are capable of chelating thorium ions in general.

7. The reference of Deal et al. was used to teach of ^{225}Ac-HEHA, DOTA and PEPA complexes used for radioimmunotherapy and to teach of studies that suggest that a thermodynamically and kinetically stable complex is formed from thorium (IV) and HEHA.

8. The reference of Larsen et al. '625 was specifically used to teach that the radionuclides ^{227}Th, ^{225}Ac or ^{223}Ra, etc. are analogously used to prepare receptor binding conjugates with oestrogen or testosterone receptor binding molecules to specifically target soft tissue sites for the treatment of cancer.

9. At the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute the thorium (IV) of Jacques et al. for the ^{227}Th of Larsen et al. as Deal et al. teaches that ^{225}Ac and thorium (IV) successfully form complexes with HEHA and/or DOTA for radioimmunotherapy and the radioactive nature of the isotope ^{227}Th changes the nuclear properties of thorium but does not change the chemical or physical properties. Thus, it would have been predictable that all thorium isotope will have the same binding characteristics and chelate to DOTA and/or HEHA.

10. Larsen et al. teaches that ^{227}Th, ^{225}Ac are analogously used for treating cancer. Thus, the substitution of thorium (IV) for ^{227}Th predictably provides for complexes that are useful for radioimmunotherapy as evidence by the equivalence of ^{225}Ac-DOTA complexes and those comprising ^{227}Th.

11. The complexes of the combined disclosures encompass the pharmaceutical composition of the instant claims, have the same properties and are capable of the same functions, such as effectively encapsulating ^{227}Th and its decay product ^{223}Ra.

12. Further, the claims are not drawn to the method of encapsulating thorium-227 and its decay product radium-223.

13. Applicant asserts that Deal discloses complexes of Actinium-225 with similar ligands to those used in Jacques. The complexes are reported to possess increased stability and reduced toxicity over free Actinium-225 and complexes of this isotope with acyclic chelators. Applicants submit that Deal simply describes the well-known chelate effect, whereby complexes of bidentate or polydentate ligands are found to be more stable than those with unidentate ligands. Applicants submit that Deal provides to the skilled worker nothing more than confirmation of general knowledge that macrocyclic complexes of radionuclides are more stable than those containing acyclic chelates and that this increased stability leads to a reduction in toxicity. Deal, however, even if combined with Jacques, fails to provide the skilled worker with the necessary teachings which would render the pending claims obvious because Deal does not describe the suitability for such chelators in administering Thorium-227 in a soft-tissue targeting form. In fact, in the left hand column at page 2991, Deal states:

[T]he extremely rapid elimination of 225Ac-HEHA from the blood may not provide an opportunity for the isotope to dissociate within this time frame and these conditions, thereby presenting the appearance of an inert complex under in vivo.

14. The reference of Deal et al. was used to teach of ^{225}Ac-HEHA, DOTA and PEPA complexes used for radioimmunotherapy and to teach of studies that suggest that a thermodynamically and kinetically stable complex is formed from thorium (IV) and HEHA. As evidenced by the applicant, Deal simply describes the well-known chelate effect, whereby complexes of bidentate or polydentate ligands are found to be more stable than those with unidentate ligands and provides to the skilled worker confirmation of general knowledge that macrocyclic complexes of radionuclides are more stable than those containing acyclic chelates and that this increased stability leads to a reduction in toxicity.

15. The reference of Jacques et al. was specifically used to teach that polyaza polycarboxylic macrocycles, DOTA and HEHA are capable of chelating thorium ions in general.

16. The reference of Larsen et al. '625 was specifically used to teach that the radionuclides ^{227}Th, ^{225}Ac or ^{223}Ra, etc. are analogously used to prepare receptor binding conjugates with oestrogen or testosterone receptor binding molecules to specifically target soft tissue sites for the treatment of cancer.

17. Therefore, at the time of the invention it would have been obvious and predictable to one ordinarily skilled in the art that the radioactive nature of the isotope ^{227}Th changes the nuclear properties of thorium but does not change the chemical or

physical properties. Thus, it would have been predictable that all thorium isotope will have the same binding characteristics and chelate to DOTA and/or HEHA, as stated by Jacques et al. and Deal et al. to provide complexes to treat cancer with reduced toxicity wherein macrocyclic complexes of radionuclides are more stable than those containing acyclic chelates and that this increased stability leads to a reduction in toxicity.

18. Further, the instant claims are not drawn to the method of administering thorium-227 in a soft-tissue targeting form.

19. Applicant asserts that the complexes described by Deal provide a carrier for the radionuclide which is stable enough to allow it to be adequately distributed around the body, but which then releases the isotope, enabling it to decay by α-emission and exert its cytotoxic effect. Deal aims to generate complexes which are stable enough to retain the radionuclide as it distributes itself around the body, but which can also eventually release the isotope. This contrasts with the complexes of the claimed invention, which are targeted and thus designed with the aim of retaining the isotope at the target site until radioactive decay. The success of the types of chelated disclosed in Deal therefore, if anything, teaches away from their suitability for use in the claimed invention.

20. The instant claims are drawn to a pharmaceutical composition and not a method of using the pharmaceutical composition.

21. The reference of Deal et al. teaches of ^{225}Ac-HEHA, DOTA and PEPA complexes used for radioimmunotherapy and teaches of studies that suggest that a thermodynamically and kinetically stable complex is formed from thorium (IV) and

HEHA. The ^{225}Ac-complexes formed with DOTA provide substantial improvement for both elimination of the isotope and decreased uptake in the liver and bone. Macrocyclic complexes of radionuclides are more stable than those containing acyclic chelates and that this increased stability leads to a reduction in toxicity. Also, Deal et al. teaches that the rapid elimination of ^{225}Ac-HEHA from the blood is positive as this doesn't provide an opportunity for the isotope to dissociate within this time frame, thereby presenting the appearance of an inert complex under in vivo. This opposes applicant's assertion that the radioisotope is released, enabling it to decay by α-emission and exert its cytotoxic effect.

22. The reference of Larsen et al. '625 was specifically used to teach that the radionuclides ^{227}Th, ^{225}Ac or ^{223}Ra, etc. are analogously used to prepare receptor binding conjugates with oestrogen or testosterone receptor binding molecules to specifically target soft tissue sites for the treatment of cancer.

23. The reference of Ma et al. was used to teach of ^{225}Ac conjugates comprising a functionalized chelant wherein the ^{225}Ac complex is covalently attached to a biological molecule (e.g. hapten, antigen, etc.) to provide for tumor specificity in the treatment of cancer.

24. At the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute the thorium (IV) of Jacques et al. for the ^{227}Th of Larsen et al. as Deal et al. teaches that ^{225}Ac and thorium (IV) successfully form complexes with HEHA and/or DOTA for radioimmunotherapy and the radioactive nature of the isotope ^{227}Th changes the nuclear properties of thorium but does not change the chemical or physical

properties. Thus, it would have been predictable that all thorium isotope will have the same binding characteristics and chelate to DOTA and/or HEHA and the substitution of thorium (IV) for ^{227}Th predictably provides for complexes that are useful for radioimmunotherapy as evidence by the equivalence of ^{225}Ac-DOTA complexes and those comprising ^{227}Th.

25. Larsen et al. teaches that ^{227}Th, ^{225}Ac are analogously used for treating cancer. Jacques et al. also teaches that thorium ions can be predictably conjugated to the DOTA chelating ligand wherein it would have been advantageous for one skilled in the art to chelate ^{227}Th to DOTA for the substantial improvement of both elimination of the isotope and decreased uptake in the liver and bone during radioimmunotherapy.

26. The complexes of the combined disclosures encompass the pharmaceutical composition of the instant claims, have the same properties and are capable of the same functions, such as tumor specificity in the treatment of cancer and retaining the isotope at the target site until radioactive decay.

27. Applicant asserts that to be effective in a targeted method, a complex must not only successfully bind thorium-227, but must also retain this binding for at least the order of the radioactive half-life if a reasonable proportion of the administered material is to have therapeutic benefit. The complexes of Deal, as is evident from the above citation, do not have these properties required for a targeting complex. As such, Deal not only does not describe complexes containing Thorium-227, the Actinium-225 complexes it does describe would also not be useful for targeting a soft tissue. Moreover, as is clearly indicated in the application as filed, prior to filing of the present

application, the understanding in the art was that Thorium-227 is not suitable for use in the treatment of soft tissue disease because the minimum therapeutic dose of Thorium-227 would generate more than the lethal dose of its daughter, Radium-223. Given that, in a soft tissue targeting complex, no way was known to control the fate of the Radium-223 daughter nuclide and keep it safely retained, it would be free to distribute around the body with potentially fatal effects on the patient. The use of Thorium-227 was therefore not considered.

28. The reference of Deal et al. teaches that the rapid elimination of ^{225}Ac-HEHA from the blood is positive as this doesn't provide an opportunity for the isotope to dissociate within this time frame, thereby presenting the appearance of an inert complex under in vivo. This opposes applicant's assertion that the radioisotope is released, enabling it to decay by α-emission and exert its cytotoxic effect. Macrocyclic complexes of radionuclides are more stable than those containing acyclic chelates and that this increased stability leads to a reduction in toxicity. Also, the ^{225}Ac-complexes formed with DOTA provide substantial improvement for both elimination of the isotope and decreased uptake in the liver and bone.

29. Larsen et al. teaches that ^{227}Th, ^{225}Ac are analogously used for treating cancer. Jacques et al. also teaches that thorium ions can be predictably conjugated to the DOTA chelating ligand wherein it would have been advantageous for one skilled in the art to chelate ^{227}Th to DOTA for the substantial improvement of both elimination of the isotope and decreased uptake in the liver and bone during radioimmunotherapy.

30. The complexes of the combined disclosures as stated above encompass the pharmaceutical composition of the instant claims, have the same properties and are capable of the same functions, such as retaining the ^{223}Ra daughter and tumor specificity in the treatment of cancer and retaining the isotope at the target site until radioactive decay.

31. Applicant asserts that it should be noted that Actinium-225 decays to Francium-221, which produces three toxic alpha decays before reaching stable Bismuth-209, whereas Thorium-227 generates Radium-223, which generates four alpha emissions before reaching stable Lead-207. Thus, on first inspection, one would expect Radium-223 to be a third more toxic than Francium-221. The nature of Radium-223 as a calcium analogue would also be significant in expected bone marrow toxicity. The issues of toxicity of the daughter nuclide would therefore be far less significant when considering the use of Actinium-225 in radioimmunotherapy. This is reflected in Deal, in which the eventual release of the Actinium-225 from the chelate is desired. Larsen '625 discloses that Astatine-211, Lead-212 (as a generator), Bismuth-212, Bismuth-213, Radium-223, Radium-224, Actinium-225, and Thorium-227 are all example of alpha-emitters. Beyond this, which has been known for decades, Larsen '625 makes no further comment on the similarity, or any other properties, of any members of this group.

32. The reference of Deal et al. was used to teach of ^{225}Ac-HEHA, DOTA and PEPA complexes used for radioimmunotherapy and studies that suggest that a thermodynamically and kinetically stable complex is formed from thorium (IV) and HEHA. The method to reduce toxicity is to “trap” the metal in a chelating agent and thus

Deal et al. is directed to improving the in vivo stability (trap the metal) to reduce toxicity. HEHA is a suitable chelator for ^{225}Ac that reduces the in vivo toxicity and has increased in vivo stability due to its maximum coordination number of 12. Deal et al. teaches that the rapid elimination of ^{225}Ac-HEHA from the blood is positive as this doesn't provide an opportunity for the isotope to dissociate within this time frame, thereby presenting the appearance of an inert complex under in vivo. This opposes applicant's assertion that the radioisotope is released, enabling it to decay by α-emission and exert its cytotoxic effect. Macrocyclic complexes of radionuclides are more stable than those containing acyclic chelates and that this increased stability leads to a reduction in toxicity. Also, ^{225}Ac-complexes formed with DOTA provide substantial improvement for both elimination of the isotope and decreased uptake in the liver and bone.

33. The reference of Larsen et al. '625 was specifically used to teach that the radionuclides ^{227}Th, ^{225}Ac or ^{223}Ra, etc. are analogously used to prepare receptor binding conjugates with oestrogen or testosterone receptor binding molecules to specifically target soft tissue sites for the treatment of cancer.

34. The chelators of the combined disclosure, as stated above, encompass the chelators of the instant claims, have the same properties and are capable of the same functions, such as retaining the daughter nuclide to reduce toxicity as evidenced by Deal et al. which teaches that macrocyclic complexes of radionuclides are more stable than those containing acyclic chelates and that this increased stability leads to a reduction in toxicity.

35. Applicant asserts that none of the cited references, either individually or in combination, teach or suggest that suitable bifunctional chelators can be attached to soft tissue targeting moieties other than folate and maintain control of the radioisotope sufficiently to be of therapeutic value.

36. Larsen et al. explicitly teaches that a receptor binding conjugates comprising a radionuclide (i.e. ^{227}Th, ^{225}Ac or ^{223}Ra, etc.) and receptor binding molecules (e.g. oestrogen or testosterone (not folate)) having affinity to breast or prostate cancer. The conjugates of the disclosure are specifically directed to the soft tissue site containing the receptor.

37. Ma et al. discloses ^{225}Ac conjugates comprising a functionalized chelant wherein the ^{225}Ac complex is covalently attached to a biological molecule (e.g. hapten, antigen, etc.) to provide for tumor specificity in the treatment of cancer.

38. At the time of the invention it would have been obvious to one ordinarily skilled in the art to utilize an oestrogen or testosterone receptor binding moiety to target the chelators of the combined disclosures, stated above, to soft tissue for the treatment of cancer as Larsen et al. and Ma et al. teach of biological molecules and/or receptor binding molecules, that are not folate or antibodies, having an affinity for soft tissue sites containing the receptors.

39. Applicant asserts that Ma teaches that the toxicity of Actinium-225 is a considerable issue with a number of known chelators. Paragraph [0005] of Ma points to this being the result of the cascade of alpha and beta emissions caused upon decay. Given that, as indicated above, Thorium-227 is known to generate one third more toxic

alpha decays before reaching a stable daughter than Actinium-225, Applicants submit that the skilled worker reading Ma would be disinclined to attempt to substitute an apparently more toxic alternative (Thorium-227) for Actinium-225.

40. The reference of Larsen et al. '625 teaches that the radionuclides ^{227}Th, ^{225}Ac or ^{223}Ra, etc. (i.e. alpha emitters) are analogously used to prepare receptor binding conjugates with oestrogen or testosterone receptor binding molecules to specifically target soft tissue sites for the treatment of cancer.

41. Many factors are considered when choosing a radionuclide for treatment of cancer, such as availability, storage, etc. and thus it would have been predictable to one or ordinary skilled in the art to choose either of the alpha emitters, ^{227}Th or ^{225}Ac based upon availability. Also, it would have been predictable to one of ordinary skill in the art to choose the alpha emitter ^{227}Th that has a longer half-life for storage and transportation purposes as it is taught above that ^{227}Th generates stable complexes with macrocycles, such as DOTA or HEHA that provide for reduced toxicity.

42. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

No claims are allowed at this time.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 7-4 M, 7-4 T, 6 Th, 7-4 F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Melissa Perreira/
Examiner, Art Unit 1618

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618